

Cefoperazone (Cefobid) for treating men with gonorrhoea caused by penicillinase producing *Neisseria gonorrhoeae*

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SUMMARY The recent emergence of spectinomycin resistant penicillinase producing *Neisseria gonorrhoeae* (PPNG) and the high prevalence of PPNG strains among the gonococcal isolates in Seoul represent a grave challenge to the programme for controlling sexually transmitted disease (STD).

Fifty men with uncomplicated gonococcal urethritis caused by PPNG strains were treated with a single intramuscular injection of 1 g cefoperazone. Forty two patients were followed up. All patients recovered including three who became reinfected and required further treatment. Two patients (4.8%) developed postgonococcal urethritis (PGU).

The MIC₉₀ of cefoperazone measured by an agar dilution susceptibility test was 0.12 mg/l.

Introduction

The ever decreasing sensitivity of *Neisseria gonorrhoeae* to various antibiotics has been noted throughout the world.¹⁻⁷ The high prevalence of penicillinase producing *Neisseria gonorrhoeae* (PPNG) strains among the isolates in Seoul has been a major problem. Spectinomycin has been recommended to treat uncomplicated gonococcal urethritis that has failed to respond to first line treatment and infections caused by PPNG strains. The recent appearance of spectinomycin resistant PPNG strains in Korea is a grave threat to the programme for controlling sexually transmitted diseases (STDs) and makes urgent an intensive search for an alternative treatment regimen.

Materials and methods

We studied men attending the STD clinic of Choong-Ku Health Center in Seoul during the four month period between March and July 1983 seeking treatment for urethral discharge. Only those patients with uncomplicated gonococcal urethritis were included in the study. A total of 699 patients attended the STD clinic during this period. Among 275 patients with gonorrhoea, 65 were found to have uncomplicated

urethritis caused by PPNG strains. Of these, 50 were treated with cefoperazone 1 g intramuscularly and 42 patients were followed up. Their ages ranged between 19 and 49; the mean age was 25.5 and the median 25. Over 85% of the patients were under 30. Of the 42 men followed up, 22 (52.4%) had received previous treatment for their gonorrhoea, and 13 had been treated with penicillin shortly before treatment with cefoperazone.

TREATMENT

Each patient was given a single intramuscular injection of cefoperazone (Cefobid) 1 g, and was advised to refrain from sexual intercourse and to avoid taking other antibiotics and alcohol.

FOLLOW UP

Each patient was asked to attend the clinic for a test of cure three to five days after treatment with cefoperazone, when urethral smears were taken for Gram staining and microscopy and for culture. Patients who failed to attend were reminded by telephone. Defaulters who failed to attend after the initial treatment were excluded from the final assessment of the results.

FAILURE OF TREATMENT

Any patient showing intracellular Gram negative diplococci on Gram stained smear microscopy or a positive culture at the follow up visit without a history of further sexual contact, or both, was re-

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garded as a treatment failure. Any patient with a recurrence who admitted having further sexual intercourse since treatment was regarded as reinfected and treated as a new case.

CRITERION OF CURE

At the follow up visit patients whose urethral smears showed no Gram negative diplococci and gave negative results on culture were considered to have been cured.

POSTGONOCOCCAL URETHRITIS (PGU)

At the follow up visit a patient was considered to have PGU if his urethral culture was negative and the smear showed more than 20 leucocytes per high power field or if there were more than 20 leucocytes per high power field in the urinary sediment after centrifuging at $600 \times g$ for 15 minutes.^{10 11 14}

DIAGNOSTIC TESTS

A urethral specimen was taken with a cotton tipped wooden stick from each patient suspected of having uncomplicated gonococcal infection, and was spread over a slide for Gram staining. Another specimen was inoculated on Thayer-Martin medium by Z rolling, kept in a candle jar, and within two hours cross streaked with a loop and incubated in a candle jar at 35-36°C for 20-48 hours. A positive oxidase reaction in colonies with typical morphology composed of Gram negative diplococci was taken as sufficient evidence of *N gonorrhoeae*. To detect β -lactamase the chromogenic cephalosporin test was used.^{8-10 12 14 15} The positive cultures were subcultured on enriched chocolate agar, to which 2 mg/l sodium penicillin G was added. The susceptibility of isolates to cefoperazone, penicillin, tetracycline, and spectinomycin was tested by the agar plate dilution method.¹³ Serological tests for syphilis were performed at the first visit.

SUSCEPTIBILITY TEST

Twofold concentrations of the antibiotics to be tested were distributed into chocolate agar supplemented with Iso-vitalex. The test organisms were suspended in Müller-Hinton broth. The suspension turbidity was adjusted to correspond to 0.5 McFarland standard barium sulphate. The suspension was further diluted 100-fold, and each test suspension was inoculated on to the plates by a replicator. The plates were incubated in a candle jar at 35°C for 24 hours. The minimum inhibitory concentration (MIC) was the lowest concentration of antibiotics that permitted the growth of no more than one colony in each MIC determination. Strain No K82-82 was used as the reference.

Results

All 42 patients were cured, including the three who became reinfected. PGU was diagnosed in two (4.8%). No side effects were reported. The serological tests for syphilis gave negative results in all cases at the first visit. The table shows the susceptibilities of 40 isolates to various antibiotics. The MICs of penicillin ranged from 4 mg/l to over 32 mg/l, with 26 (65%) of the 40 isolates having MICs of ≥ 32 mg/l. The MICs of tetracycline were between 0.25 mg/l and 8 mg/l. The results showed that 80% of strains were resistant to tetracycline. The MICs of spectinomycin ranged from 4 mg/l to 16 mg/l. Cefoperazone MIC ranged between <0.015 mg/l to >0.24 mg/l, with 34 (85%) of the 40 isolates having MICs of up to 0.06 mg/l. The MIC₉₀ of cefoperazone was 0.12 mg/l.

TABLE Minimum inhibitory concentrations* of cefoperazone and three other antibiotics for 40 isolates of PPNG strains

Concentrations (mg/l)	No (%) of strains inhibited by:			
	Cefoperazone	Tetracycline	Penicillin	Spectinomycin
<0.015	5 (12.5)			
0.015	6 (15)			
0.03	7 (17.5)			
0.06	16 (40)			
0.12	4 (10)			
0.24	1 (2.5)			
>0.24	1 (2.5)			
0.25		2 (5)		
0.5		6 (15)		
1		4 (10)		
2		6 (15)		
4		14 (35)	1 (2.5)	7 (17.5)
8		8 (20)	2 (5)	15 (37.5)
16			11 (27.5)	18 (45)
32			6 (15)	
>32			20 (50)	

* The lowest concentration of antibiotics that permitted the growth of no more than one colony in each MIC determination.

PPNG = penicillinase producing *N gonorrhoeae*.

Discussion

The appearance of PPNG strains in 1976^{16 17} threatened the control of STD, which had already been complicated by decreased susceptibility of *N gonorrhoeae* to penicillins and other antibiotics.^{1-10 14} Spectinomycin is still useful against PPNG strains but spectinomycin resistant PPNG strains have already been reported in Korea^{19 20} and in other countries,²¹ leading to fear that the days of spectinomycin resistant *N gonorrhoeae* predominance might not be too far away. New reliable treatment regimens therefore have to be sought.

Gentamicin, chloramphenicol, thiamphenicol, and traditional treatment regimens using penicillins and tetracyclines have been tried and found to be ineffective in Seoul.²²⁻²³ In previous publications we reported the sudden upsurge of PPNG strains among the isolates of *N gonorrhoeae* in 1981 and the continued high prevalence of PPNG strains thereafter in Seoul.^{9 10 14 22}

The strains of *N gonorrhoeae* isolated in South East Asia generally show low sensitivity to antibiotics.⁵ Korean strains show similar, if not lower, sensitivities to various antibiotics that have higher MICs for Korean strains than for those from Singapore reported by Sng *et al.*² We compared our susceptibility test results with those of South East Asia and Singapore. The MIC of penicillin for our strains is considerably higher than for South East Asian strains; the MIC of tetracycline is slightly higher for our strains than South East Asian strains and even those from Singapore; and the MIC of spectinomycin is similar for strains from all three regions.

In previous work on the treatment of men with uncomplicated urethritis caused by PPNG we found that a single intramuscular injection of cefoperazone 0.5 g gave good results, with a failure rate of 4.8%.¹⁴ In this study we increased the dose to 1 g and found the effect to be excellent. All 42 cases were cured with a single injection of cefoperazone 1 g, and no side effects were detected. This suggests that cefoperazone 1 g by intramuscular injection is an excellent drug for the treatment of gonococcal urethritis caused by PPNG strains. A single injection of cefotaxime 1 g gave similar results,¹⁰ but required the concomitant use of 1 g probenecid, which might cause disturbances of the upper gastrointestinal tract.¹⁸

In the face of increased resistance of *N gonorrhoeae* and high prevalence of PPNG strains among the isolates, especially PPNG strains resistant to spectinomycin, cefoperazone is an excellent alternative to spectinomycin in the treatment of urethritis caused by PPNG strains. The treatment is well tolerated and no side effects have been noted.

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